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PHASE 3 SUMMARY OF MRID 00149532 AND RELATED MRIDS 00145793 AND 00149531:

TWO-GENERATION REPRODUCTION STUDY IN RATS

STUDY # 281023

FLUMETRALIN

GUIDELINE REFERENCE:

83-4 2-GENERATION REPRODUCTION - RAT

SUMMARY PREPARED BY:

MERRILL TISDEL

5 OCTOBER 1990

ORIGINAL STUDY PREPARED BY:

SCIENCE APPLICATIONS, INC.

LA JOLLA, CALIFORNIA

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Company: CIBA-GEIGY Corporation (Typed Name)

Company Agent: Thomas Parshley (Typed Name)

Title: Senior Reg. Specialist

Signature: _____ Date: _____

These data are the property of the Agricultural Division of CIBA-GEIGY Corporation, and as such, are considered to be confidential for all purposes other than compliance with FIFRA §10. Submission of these data in compliance with FIFRA does not constitute a waiver of any right to confidentiality which may exist under any other statute or in any other country.

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GOOD LABORATORY PRACTICE STATEMENT

Science Applications, Inc. is no longer conducting toxicology business. Therefore, a GLP statement cannot be obtained from a study director or laboratory management. The attached pages from the report on this study indicate that the study was conducted under FDA Good Laboratory Practice Regulations (21 CFR 58).

GOOD LABORATORY PRACTICE STATEMENT

This study does not meet the requirements for 40 CFR Part 160 (see above).

Submitter/Sponsor of Study: Merrill Tisdel

Merrill Tisdel
Agricultural Division
CIBA-GEIGY Corporation
Greensboro, North Carolina

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SCIENCE APPLICATIONS, INC.

QUALITY ASSURANCE STUDY INSPECTION AND COMPLIANCE STATEMENT

STUDY TITLE: Two Generation Reproduction Study of CGA-41065 Technical in Albino Rats

PROJECT NUMBER: 281023

QUALITY ASSURANCE STATEMENT:

Quality Assurance inspections were conducted in compliance with Good Laboratory Practice Regulations currently in effect and published in the Federal Register, Volume 43, December 22, 1978. The following study phases and final report were inspected according to this Quality Assurance Unit's Standard Operating Procedures, and the findings were reported to the Study Director on the following dates:

Date of Inspection	Study Phase	Findings Reported	QA Officer
12/11/81	Animal Receipt	Not Reported	S.Keener
12/31/81	Protocol Compliance	1/4/82	S.Keener
01/13/82	Animals Records, Animal Identification, Randomization, Food Consumption, Body Weights and Clinical Observations	1/13/82	S.Keener
01/25/82	Diet Formulation	1/25/82	S.Keener
02/17/82	Diet Formulation Analyses	2/17/82	S.Keener
03/01/82	Diet Formulation	3/1/82	S.Keener
03/09/82	Clinicals, Body Weights and Food Consumption	3/9/82	S.Keener
04/14/82	F_0 Breeding, Smearing	4/23/82	S.Keener
05/05/82	Litter Processing	5/05/82	S.Keener
06/01/82	F_0, F_{1a} Sacrifices and Necropsies	6/2/82	S.Keener
06/11/82	F_1 Randomization and Animal Identification	6/14/82	M.Grismer
06/21/83	Diet Formulation	6/21/82	M.Grismer
6/23/82	Body Weights, Clinical Observations, and Food Consumption	6/23/82	M.Grismer
07/27/82	Histology Laboratory	8/2/82	S.Keener
08/02/82	Diet Formulation	8/2/82	S.Keener
10/20/82	Food Consumption, Body Weights and Clinical Observations	10/20/82	M.Grismer

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10/26/82	Breeding for F_{2a}	10/26/82	M. Grismer
11/11/82	Diet Formulation Analyses	11/15/82	S. Keener
11/17/82	F_{2a} Pup Weights and Deliveries	11/17/82	M. Grismer
12/09/82	F_{2a} Weanlings Necropsies	12/22/82	M. Grismer
01/19/83	Breeding for F_{2b}	1/19/83	M. Grismer
02/04/83	F_1 Male Sacrifices	2/14/83	S. Keener
02/09/83	F_{2b} Deliveries and Pup Weights, Diet Formulation	2/14/83	S. Keener
02/23/83	F_1 Female and F_{2b} Necropsies	2/23/83	S. Keener
05/20/83 - 06/23/83	Study Notebook Audit	6/23/83	D. May
10/31/83 - 11/16/83	Draft Final Report Audit	11/16/83	D. May and J. White
02/27/85	Final Report Audit	02/27/85	E. Gallagher

Raw Data including any specimens, and the final report are archived with the Division of Toxicology, Science Applications, Inc. test facility.

Eileen S. Gallagher
for Denice E. May
Denice E. May, M.S.
Quality Assurance Officer

2/27/85
Date

CGA/SAI 281023

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Certification of Availability of Raw Data

I hereby certify that the submitter possesses or has access to the raw data used in or generated by the study summarized in this document.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

Certification of Accuracy of Summary and Adequacy of the Study

I certify, in compliance with FIFRA section 4(e)(1)(A), that this summary accurately represents the data presented in the report(s) of this study cited by MRID, and that this study fully satisfies all pertinent requirements of the OPP Guideline it addresses.

Submitter's Representative:

Signature/Date: Merrill Tisdel 10.15.90

Typed Name: Merrill Tisdel

Title: Toxicologist

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83-4 Reproduction

ACCEPTANCE CRITERIA

Does your study meet the following acceptance criteria?

1. Y — Technical form of the active ingredient tested.
2. N — At least 20 males and sufficient females to yield 20 pregnant /dose group
3. Y — At least 3 dose groups and a control.
4. Y — At the high dose, parental toxicity is observed (or a limit dose is given, 1,000 mg/kg/day).
5.* Y — At the low dose, no reproductive effects are observed.
6.* Y — Analysis for test material stability, homogeneity and concentration in dosing medium
7. N — P_1 animals 8 weeks old at the start of the study.
8. Y — Dosing is continuous starting with the P_1 animals until an individual animal is sacrificed.
9. N — Mating is 1 male to 1 female.
10. Y — The mating period is not more than 3 weeks.
11. Y — At least two generations are bred.
12. Y — Individual daily observations.
13. Y — Individual body weights.
14. Y — Individual food consumption.
15. Y — Individual litter observations.
16. Y — Individual litter weights (pup weights) at birth and on days 4, 7 (optional), 14 and 21 .
17.* Y/N — Sacrifice schedule, all mating males immediately after last mating, all breeding females immediately after weaning last litter, all animals not used for breeding immediately after weaning.
18.* Y/N — Necropsy on all animals
19.* Y — Histopathology of reproductive organs from all animals on the high dose and control P_1 and F_1 animals selected for mating. Animals from all other dosing groups if histological effects are observed at the high dose.
20.* N — Histopathology of all organs with gross lesions.

Criteria marked with a * are supplemental and may not be required for every study.

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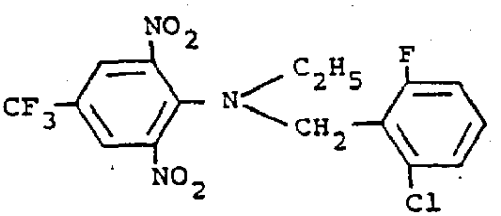
IDENTIFICATION OF TEST MATERIAL

Chemical Name

CAS Name:	N-(2-Chloro-6-fluorobenzyl)-N-ethyl-α,α,α,-trifluoro-2,6-dinitro-p-toluidine or 2-Chloro-N-[2,6-dinitro-4-(trifluoromethyl)phenyl]-N-ethyl-6-fluorobenzenemethanamine
Common Name:	Flumetralin
Trade Name:	Prime +®
CIBA-GEIGY Code Number:	CGA-41065
CAS Registry Number:	62924-70-3
EPA Shaughnessy Number:	Unknown

Chemical Structure:



Percent Active Ingredient

92% minimum

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Flumetralin: 83-4: Reproduction Study in Rats

1. The test material was Flumetralin (CGA-41065) Technical, FL-810973, purity 96.4%.

2. Charles River rats, CRL:CD® (SD)BR, were fed diets containing 0, 30, 300, 1000, or 1500 ppm of Flumetralin Technical. There were 15 males and 30 females per group (dose) for each of two generations. There was one litter from the F_0 parents and there were two litters from the F_1 parents, F_0 (F_1a) and F_1 (F_2a and F_2b).

3. At the initiation of treatment, the F_0 males and females were five weeks of age.

4. Signs of toxicity in the high-dose group included decreased body weight gain during premating and gestation for F_1 females and decreased body weight and food consumption in the F_1 females. At necropsy, yellowish fat tissue was noted in most male and female F_0 and F_1 parental animals.

5. The no-observable-effect level for reproductive toxicity was 1500 ppm Flumetralin Technical in the diet.

6. Homogeneity and stability of the test material in Purina Certified Rodent Chow® (30 and 1500 ppm) were determined prior to study initiation. Concentration of Flumetralin in the diet was determined at approximately monthly intervals for all dose levels. The test material was found to be homogeneously distributed in the diet and was stable for at least two weeks at room temperature. Assay concentrations were approximately 96%, 95%, 94%, and 102% for the 30, 300, 1000, and 1500 ppm diets, respectively.

7. The treatment was continuous (seven days/week) for two parental generations of animals and their offspring. The F_0 generation received test diets from study initiation through sacrifice after weaning of the F_1 litters (23 weeks on test). F_1 parental animals received test diets from weaning through sacrifice after weaning of the F_2b litters.

8. One male was mated with two females from the same group. Animals were cohabited for up to 14 days for F_0 animals and up to 21 days for F_1 animals. Males which failed to copulate within two estrus cycles (eight days for F_0 and ten days for F_1) were replaced with a different males from the same group. Cohabitants were selected at random, with sibling pairings being avoided. Sperm on a vaginal smear or copulatory plug (when appropriate) was used as evidence of positive mating.

9. Flumetralin Technical was administered in the feed continuously to four groups of male and female rats at four dose levels for two successive generations [F_0 (F_1a litter) and F_1 (F_2a, F_2b litters)]. A fifth group of rats received the untreated diet for two successive generations and served as concurrent controls.

10. All animals were observed for mortality at least twice daily during the weekdays and once daily on the weekends. Clinical observations were made twice daily and recorded weekly. All male and female parental animals in the 300, 1000, and 1500 ppm groups had yellow-orange colored urine, which was presumed to have resulted from the ingestion of Flumetralin in the diet. Other noted clinical signs were not considered treatment-related.

11. F_0 males and females were weighed weekly throughout the premating and mating periods. During gestation, sperm-positive females were weighed on Days 0, 7, and 14; the day of parturition; and postpartum Days 7, 14, and 21. After the mating period, the unmated females and males were weighed monthly until sacrifice. F_1 males and females were weighed on a similar schedule, and in addition, were weighed weekly during the rest period between F_2a and F_2b litters.

    There were no statistically significant differences in body weights among F_0 males during the premating period. Body weights for 1500 ppm and 1000 ppm F_0 females were significantly lower than the control weight at Week 15 of the premating period, and the weight gains through Week 15 were 87% and 90% of the control, respectively. The weight gains of F_0 females through gestation were 88% and 89% for the 30 and 300 ppm groups, respectively, but only 69% and 78% for the 1000 and 1500 ppm groups, respectively, when compared to the control.

    There were no significant differences in weights among F_1 males during the premating period, although the weight gain through Week 18 was 89% of the control. Body weight throughout the premating period was significantly lower than the control for the 1500 ppm females, and also during most weeks

for the 1000 ppm females. Body weights remained lower for 1000 and 1500 ppm females throughout the F_2a gestation and for most time points during the F_2b gestation.

12. Food consumption determinations were made weekly during the premating periods for F_0 (15 weeks) and F_1 (18 weeks) parental animals. There were no differences in food consumption for F_0 males and females or for F_1 males. Food consumption for 1000 and 1500 ppm females was generally slightly lower during most weeks of the premating period when compared to the control values.

13. On the day of parturition, the number of pups born, live and dead, were recorded. Pups were observed twice daily for mortalities and changes in physical appearance.

    The number of pups born per litter and the number born alive were comparable among the groups for the F_1a, F_2a, and F_2b litters. No treatment-related structural anomalies were noted in any of the litters. There were no treatment-related effects on survival throughout the lactation period.

14. Pups were weighed on the day of parturition, and also on Days 4, 7, 14, and 21 of lactation. There were no statistically significant differences in weights among the groups for the F_1a, F_2a, and F_2b litters. There were also no significant differences in sex ratios (M:F).

15. All surviving F_0 males and females were sacrificed after weaning of the F_1a litters, Week 34. F_1a animals not selected as F_1 parental animals were sacrificed after weaning. F_1 parental males and females were sacrificed after weaning of F_2b litters. F_2a weanlings were sacrificed on Day 21 postpartum. F_2b weanlings were sacrificed on Day 21 postpartum.

16. All F_0 animals that died were necropsied and gross lesions collected and retained. All surviving F_0 males and females were necropsied; testes were collected from all males.

    Five F_1a weanlings per sex in each group were necropsied and the organs weighed. An additional five F_1a weanlings were necropsied for gross lesions. When no treatment-related lesions were observed, the remaining F_1a weanlings which were not selected as F_1 parents were examined externally for abnormalities and discarded.

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All F_1 parental animals were necropsied. Ten males and 25 females in each group were randomly selected for organ weights and tissue collection.

All F_2a weanlings were necropsied for gross lesions and discarded.

All F_2b weanlings were necropsied. Five weanlings per sex in each group were randomly selected for organ weights and tissue collection.

During the necropsies, the external surfaces; all orifices; the cranial, thoracic, abdominal, and pelvic cavities; the external and cut surfaces of the spinal cord; the brain; cervical tissue; the carcass; and the internal organs were examined.

The heart, brain, liver, kidneys, testes or ovaries, and prostate or uterus were weighed from animals indicated above.

Yellow-colored fat tissue was noted in a number of F_0 females and F_1 males and females in the 300 ppm group, and in most F_0 and F_1 males and females in the 1000 and 1500 ppm groups. There were no other treatment-related necropsy findings in F_0 or F_1 parental animals or in any of the F_1a, F_2a, or F_2b litters. There were no significant differences among groups for any of the organ weight measurements made.

17. Testes and epididymides were examined histologically from all F_0 males. The following tissues were examined from five F_1a weanlings per sex from each group, from ten F_1 parental males and 25 F_1 parental females, and from five F_2b weanlings per sex from each group: adrenal glands, bone marrow, brain, esophagus, eyes, gonads, heart, kidneys, large intestine, liver, pancreas, parathyroid, peripheral nerve, pituitary, prostate, salivary gland, skin, small intestine, spinal cord, spleen, stomach, thymus, thyroid, trachea, urinary bladder, uterus, lungs with mainstem bronchi, lymph nodes, mammary gland, muscle, and tissues with gross lesions.

The incidence and severity of lesions noted were low in all dose groups and there were no differences between the treated and control animals.

18. There were no significant changes from the Acceptance Criteria in this study. A number of minor deviations from the Criteria had no impact on the evaluation of the test material for reproductive effects in rats. There were 15 males instead of 20 (Item 2), and they were mated one male to two females (Item 9) with 30 females in each group, instead of one to one. This is considered to be a sufficient number

of males to evaluate possible effects, especially considering that there were two litters from the F_1 parents. The P_1 (F_0) parents were five weeks of age at initiation (Item 7) instead of eight, but animals were treated for 15 weeks before mating, and normal reproduction occurred in control and treated groups. For Item 17, males were not sacrificed immediately after mating, but they were not held an inordinate amount of time before sacrifice and necropsy. Not all of the F_1a weanlings were necropsied (Item 18), but a representative number were necropsied from each group of those not selected to be F_1 parents. All other animals in the study were necropsied. For Item 20, not all gross lesions were identified at necropsies. However, there was no indication from necropsy data that any treatment-related lesions were present that would not be identified from the considerable number of animals examined from the various litters and parents. In addition, in a reproductive study with no indication of effects on reproductive performance, these data would be considered supplemental.

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